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CHEMICAL ABSTRACTS, vol. 74, no. 15, 12-04-1971, page 306, column 2, abstract 74827z Columbus, Ohio, US L.J. ZANEVELD: "Synthetic enzyme inhibitors as antifertility agents" UNLISTED DRUGS, vol. 24, April 1972, page 57 Chatham New Jersey US

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DIE PHARMAZIE, vol. 28, May 1973, Berlin DD G. WAGNER et al.: "Synthese antiproteolytisch wirksamer Ester von Guanidinobenzoesäuren und Guanidinomethylbenzoesäuren", pages 293-296
DERWENT JAPANESE PATENT REPORT, vol. T/11, no. 28, 1972, London GB UNLISTED DRUGS, vol. 24, April 1972, page 53,Chatham, New Jersey,US, Abstract C
DIE PHARMAZIE, vol. 25, September 1970 Berlin DD F. MARKWARDT et al.: "Hemmung der Thrombin-, Plasmin- und Trypsinwirkung durch Alkyl- und Alkoxybenzamidine", pages 551-554

Courier Press, Leamington Spa, England.

EP 0 024 781 B1

Description

This invention relates to intrauterine devices, and more particularly to an improved intrauterine device providing a contraceptive, anti-fibrinolytic, and anti-proteolytic action when inserted in the uterus.

Many forms and configurations of intrauterine devices designed to prevent conception in the female have heretofore beein utilized. Such devices have been provided in a variety of shapes, such as the "T" device shown in U.S. Patent 3,533,406, the Loop, such as shown in Patent 3,200,815, a "Y" configuration, generally termed a "Ypsilon" configuration a ring or modified ring such as the Ota ring, and many modifications thereto, including flat, leaf-like members between various segments of the intrauterine device. Such intrauterine devices which were not provided with any medications associated therewith depended upon their presence in the uterus to prevent conception.

Further, other intrauterine devices (IUDs) have incorporated a controlled release rate medication or drug therein to further aid the anticonceptive action thereof. Such medicated IUDs have generally employed copper or progesterone as the contraceptive or antifertility agent. However, it has been found that copper-releasing intrauterine devices, as well as non-medicated intrauterine devices still resulted in pain and cramping to the wearer, as well as metrorrhagia and menorrhagia. Consequently, the excessive uterine hemorrage, with or without pain, continues to be a leading cause for this type of intrauterine device removal. The progesterone-releasing intrauterine devices are associated with significantly less bleeding than other devices but they appear to be associated with a serious complication apparently produced by the release of progesterone. This complication is ectopic pregnancy.

Nevertheless, the general convenience and safety of intrauterine devices continues to give hope that the IUD may one day provide an ideal method for worldwide population control, since it has been found, statistically, that intrauterine devices can provide effective contraception in a 98—99% range of effectivity, they do not require conscious effort, are less subject to human failings than any other type of contraceptive, their antifertility effect is completely reversible, they have minimal, if any systemic effect, and their effect is confined essentially to the uterus. However, it is believed that even greater antifertility effect can be achieved by utilizing other anticonceptic agents with an IUD, which agents do not have the serious detrimental side effects noted above.

Consequently, there has been a need for improved medicate intrauterine devices providing greater antifertility effect and in which the side effects of pain, metrorrhagia and/or menorrhagi are reduced or eliminated, and which are not associated with other serious side effects such as ectopic pregnancy.

While the inflammatory response of the endometrium to intrauterine devices has heretofore been known, I have discovered that the chronic response of the endometrium to long-term intrauterine device exposure is more a humoral type of reaction (accompanied by increased vascular permeability with edema and interstitial hemorrhage) than the immunologic or cellular type of response (accompanied by infiltration of immune complexes or of leukocytes, such as plasma cells or neutrophils). However, I have found that there are defects in small endometrial vessels which suggest damage caused by mechanical distortion of the uterine tissues. The defects generally lack hemostatic plugs of platelets and/or fibrin. Further, there is evidence that fibrinolysis is activated in the uterus in response to the presence of an intrauterine device. This activation could result in blockage of normal hemostatic reaction at several levels in the coagulation system. Further, it may initiate, aid, or aggravate humoral inflammation by any one or all of the following mechanisms:

1. Activation of the complement system and histamine release;
2. Activation of prekallikrein; and
3. Release of fibrin degradation fragments.

Histamine can cause vascular dilation and increase vascular permeability. Kallikrein (activated prekallikrein) releases bradykinin which can have an effect similar to histamine and may also cause cramping and pain. Fibrin degradation fragments may enhance the vascular effects of histamine and bradykinin. Combined with distortion of the endometrium caused by myometrial contractility around the relatively inelastic or unyielding IUD, which may also be associated with increased prostaglandin synthesis and release, it may be predicted that excessive bleeding from leaky or broken vessels will occur. For these reasons, incorporation into medicated IUD devices of potent inhibitors of plasminogen activation and plasmin activity (fibrinolytic activity for the purposes of intrauterine release over an extended time period can provide an alleviation of the aforesaid undesired effects.

It has also heretofore been found that IUD associated uterine hemmorhage can be alleviated by the systemic (oral) intake of the fibrinolytic inhibitors epsilon aminocaproic acid (EMCA) and tranexamic acid. I have also demonstrated that an EACA loaded IUD inserted into the uterus of rhesus monkeys provides an ameliorative effect on menstral blood loss, and there was no apparent systemic effect by such medicated devices on fibrinolytic activity in these animals. However, neither EACA nor tranexamic acid would apear to be satisfactory agents for long-term intrauterine medication. First, they are not highly potent anti-fibrinolytic agents and would have to be delivered at a rather high rate into the uterine cavity. Thus, a drug loaded IUD would become exhausted of its medication in a short period of time, or would require an unacceptably large size of device. In addition, EACA and tranexamic acid are

small molecules which are highly diffusible and water soluble. Therefore, intrauterine release thereof from a medicated intrauterine device at a steady, constant rate is difficult to control and effective concentrations inside the uterus difficult to maintain. Consequently, inhibitor concentrations of either EACA and tranexamic acid of between 1×10^{-3} and 1×10^{-4} Mol/liter, which is the concentration of these drugs required to be effective, respectively, over a prolonged period of time is generally not achievable considering the amount of medication which is feasible to load into an IUD and considering the diffusion and solubility properties of these compounds and the rate of water turnover inside the uterus.

While there heretofore has been some indication that certain compounds used for treatment of protozoal, bacterial and fungal infections may have anti-fibrinolytic properties there has not heretofore been any indication of anti-fertility action of these compounds added to an intrauterine device. These compounds may be generally defined as the aromatic amidines, and in particular, the aromatic diamidines. However, heretofore, it has not been specifically recognized that their anti-fibrinolytic action inside the uterus can alleviate the metrorrhagia and menorrhagia. Further, even though such metrorrhagia and menorrhagia may be alleviated, the pain and cramps associated with intrauterine devices could still remain a major drawback to effective extensive use of medicated intrauterine devices as a population control technique.

Additionally, in many prior art IUDs, expulsion thereof is a somewhat frequent occurrence. Such undesired expulsion is another drawback of prior art IUDs.

Consequently, there has long been a need for a medicated intraterine device which not only enhances the anti-fertility action of the IUD but also provides reduction or elimination of metrorrhagia or menorrhagia for an extended period of time, as well as decreasing the pain and cramps associated with wearing an intrauterine device, as well as decreasing the tendency of expulsion thereof.

I have discovered that the structure associated with the use of the amidines such as the aromatic and non-aromatic monoamidines and diamidines for utilization in connection with an IUD may provide the above desiderata. I have also discovered that the guanidines, such as aromatic monoguanidine, aromatic diguanidines, non-aromatic monoguanidines and non-aromatic diguanidines also may provide the above desiderata.

Contraceptive effects of certain guanidine and anidine compounds and groups of compounds are disclosed in:

"CHEMICAL ABSTRACTS" Vol. 74, abstract No. 74827z,

"UNLISTED DRUGS", Vol. 24, page 57, abstract a

and "UNLISTED DRUGS", Vol. 24, page 53, abstract c.

"DIE PHARMAZIE", Vol. 25, pages 551—554 and Vol. 28 pages 293—6 disclose antiproteolytic properties of guanidine and amidine derivatives.

FR—A—2 250 520

and US—A— 4 144 317 disclose intrauterine devices which controllably release contraceptive agents.

Accordingly, it is an object of the present invention to provide an improved intrauterine device.

According to the present invention I provide a medicated intrauterine device of the type insertable in the uterus said device having a controlled rate of release of said medicament and comprising a body member at least a portion of which comprises a polymer matrix incorporating said medicament characterised in that the medicament is a drug comprising an amidine and/or a guanidine or an ester or salt thereof which is capable of exhibiting an anti-proteolytic, an anti-fibrinolytic and anti-conceptive effect when released at said controlled rate.

The controlled rate is preferably 50 to 200 μg per day.

Preferably, the drug comprises:

(a) an amidine;

(b) a mixture of an amidine and a guanidine;

(c) a mixture of more than one amidine and a guanidine;

(d) a mixture of an amidine and more than one guanidine;

(e) a mixture of more than one amidine and more than one guanidine;

(f) a guanidine; and

(g) a mixture of more than one guanidine.

The anti-preoteolytic action and, in particular, the anti-fibrinolytic action of the aromatic monoamidines, aromatic diamidines and non-aromatic diamidines can provide a reduction in metrorrhagia and menorrhagia because of the particular characteristics associated with the reaction of the endometrium and/or the fluid of the uterus to the presence of an intrauterine device. Further, it is believed that inhibition of other proteolytic systems in the endometrium and/or muscle wall of the uterus can reduce and/or eliminate the pain and cramps associated with wearing an intrauterine device, as well as minimizing the risk of expulsion thereof. The amidines and, in particular the aromatic monoamidines, aromatic diamidines, and non-aromatic diamidines, have been found to possess the desired properties, due to the antifibrinolytic and other antiproteolytic effect thereof, to reduce or eliminate metrorrhagia and/or menorrhagia.

Additionally, I have discovered that there is a surprising and unexpected result in utilization of

aromatic diamidines with intrauterine devices in that they may enhance the anti-fertility effect of the IUD. That is, they may cause a greater contraceptive effect than has heretofore been obtainable with prior art IUDs of either the plain or medicated type. This unexpected result, it is believed, is achieved by the mechanism of the aromatic diamidine acting upon the fertilized egg or the blastocyst (preimplantation embryo) to cause it to degenerate. The aromatic diamidine could, in addition, act on the sperm to either kill or render them ineffective in fertilization.

I have also discovered that the guanidines, in addition to the amidines, have such properties and, it is believed, may have even more potent effects.

Thus, I have discovered that there is a surprising and unexpected result in utilization of guanidines with intrauterine devices in that they may decrease IUD induced uterine bleeding and enhance the anti-fertility effect of the IUD by providing an anti-proteolytic and, particularly, an anti-fibrinolytic action in the uterus. Each treated IUD, therefore, may additionally cause a greater contraceptive effect than has heretofore been obtainable with the above-mentioned prior art IUDs of either the plain or medicated type. This unexpected result, it is believed, is achieved by the mechanism of the guanidine acting upon the fertilized egg or the blastocyst (preimplantation embryo) to cause it to degenerate. The guanidine could, in addition act on the sperm to either kill or render them ineffective in fertilization.

Further it is believed, that certain anti-proteolytic action of the aromatic diamidines and guanidines could reduce or eliminate the pain and cramps often associated with wearing an IUD.

The body member may be of any desired shape or configuration of an intrauterine device, such as those heretofore utilized, or any other suitable configuration. A drug which may be one or more drugs selected from the class consisting or aromatic monoamidines, aromatic diamidines and non-aromatic diamidines or a drug which may be one or more drugs selected from the class consisting of aromatic monoguanidines, aromatic diguanidines, non-aromatic monoguanidines and non-aromatic diguanidines or a mixture of one or more guanidines with one or more amidines, is provided with the body member in such a fashion that its release rate over an extended period of time is controlled within predetermined limits. As utilised herein, the term "drug" refers to either a single one of the above-mentioned amidines or a mixture of more than one of the amidines, or a single one of the above-mentioned guanidines or a mixture of more than one of the gunaidines, or mixture of one or more of the amidines as set forth above with the guanidine. The body member of the intrauterine device may be a polymer matrix fabricated in any of the above-mentioned shapes or configurations from, for example, polyethylene, and the drug may, in this embodiment, be a simple mixture with the polymer matrix. The shape, charge, and other characteristics such as hydrophobicity of the molecule of the drug, as well as the characteristics of the polymer matrix of the body member can be adjusted to determine the rate of drug release from the device when placed within the uterus to achieve a desired rate of emission of the drug over a predetermined time period by known techniques.

In another embodiment of the present invention, the drug is provided as a biodegradable polymer or copolymer with for example, another amidine, guanidine and/or epsilan aminocaproic acid, and mixed with the supporting polymer matrix of the body member.

In yet another embodiment of the present invention, the drug may be provided in a biodegradable polymer or copolymer, and bonded covalently or non-covalently to the polymer matrix of the device either within or on the surface of the polymer matrix of the body member.

Additionally, in yet other embodiments of the present invention, the above-mentioned embodiments may be combined with a surface coating on the body member wherein the surface coating comprises a biodegradable cross-linked polymer or copolymer of the drug bonded covalently to the surface. Such embodiments may provide a soft hydrogel coating which enhances the tolerance of the walls of the uterus to enhance the retention of the medicated intrauterine device in the uterus during the time period soon after insertion. It has been found that the undesired expulsion often occurs during this time period.

In yet another embodiment of the present invention which may be combined with any of the above embodiments, a coating is provided on some or all of the surfaces of the body member. The coating may be covalently bonded to the surface of the body member and consists of a non-biodegradable monomer, dimer, oligomer, or cross-linked polymer of the drug. Such embodiment provides a prolonged surface effect for reducing deleterious effects on the uterine wall, as well as providing the desired prolonged release of the drug from the body member. The bleeding of the endometrium in contact with the intrauterine device is at the surface of the endometrium. The inhibition of plasminogen activator and plasmin by solid phase enzyme inhibitors such as the surface linked drugs described in this paragraph constantly during the duration of wearing of the intrauterine device could lead to a lessening of the bleeding at the interface between the endometrium and the intrauterine device.

In another embodiment of the present invention, the surface of the body member of any one of the above-defined embodiments may be partially covered by metallic copper to provide additional anti-conceptive action for the device.

The drug may be utilised either in its base form, or as certain esters such as isethionate, or as certain salts, such as hydrochloride or phosphate, depending upon the degree of solubility desired in the uterine fluid for control of release rate and tissue uptake of the drug, as well as enhancing the effectiveness of the particular compound employed.

In those embodiments of the present invention wherein a drug is provided as a coating on the surface of the IUD, the body member of the IUD may also incorporate a drug according to the principles of the present invention mixed therewith or the drug may be provided only in the coating. In those embodiments wherein a drug is provided as a coating on the surface of the IUD and a drug is also incorporated in the body member, the drug of the coating may be the same as the drug in the body member or they may be different drugs.

Reference is now made to the accompanying drawings wherein similar reference characters refer to similar elemets throughout and in which:

Figure 1 illustrates one embodiment of an intrauterine device useful in the practice of the present invention;

Figure 2 illustrates another embodiment of an intrauterine device useful in the practice of the present invention;

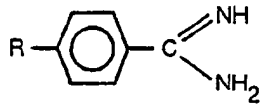
Figure 3 illustrates another embodiment of an intrauterine device useful in the practice of the present invention;

Figure 4 illustrates another embodiment of an intrauterine device useful in the practice of the present invention; and

Figure 5 illustrates another embodiment of an intrauterine device useful in the practice of the present invention.

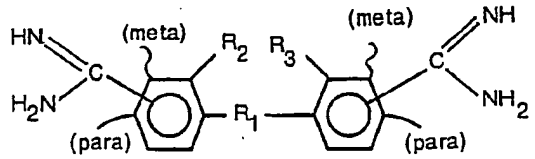
As noted above, the present invention is a medicated intraterine device wherein a preselected drug is provided with the body member of the intrauterine device. As utilised herein and in the appended caims, the term "drug" refers to one or a mixture of more than one of a preselected compound. The preselected compounds of the present invention are the amidines and in particular the aromatic monoamidines, aromatic diamidines, and non-aromatic diamidines and the guanidines and in particular the aromatic monoguanidines, the aromatic diguanidines, and non-aromatic monoguanidines, and the non-aromatic diguanidines.

The aromatic amidines may be an aromatic monoamidine of the general formula:

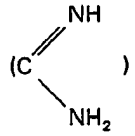


wherein:

R is a carbon chain or an aromatic group or an aromatic group with or without other elements, or, as preferred for utilization in the invention herein, an aromatic diamidine of the general formula:



in which each amidine group



may be substituted in either a meta or para position with respect to R_1.

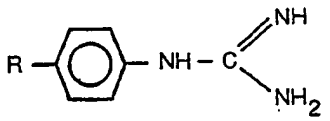
wherein:

R_1 is generally a carbon chain with or without ether bonds to the benzene rings;

R_2 and R_3 can be hydrogen, chlorine, bromine, iodine, hydroxyl group, alkyl, or other group; and

represents the benzene ring.

The aromatic guanidines may be an aromatic monoguanidine of the general formula:

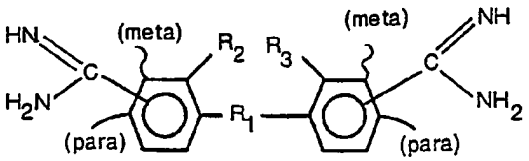


wherein:

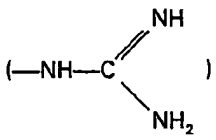
R is a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfer, etc.); an aromatic group (such as benzene) with or without additional carbons, carbon chains, and other elements; a cyclic non-aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination; and

represents the benzene ring.

As preferred for utilization in the invention herein, there may be utilized an aromatic diguanidine of the general formula:



in which each guanidine group:



may be substituted in either a meta or para position with respect to R_1, and wherein:

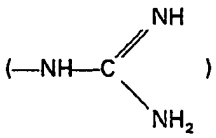
R_1 is generally a hydrocarbon chain with or without ether or ester bonds to the benzene rings;

R_2 and R_3 can be hydrogen, chlorine, bromine, iodine, hydroxyl group, alkyl, or other group; and

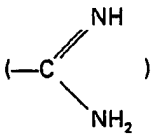
represents the benzene ring.

Table I below lists particular aromatic diamidines useful in the practice of the present invention.

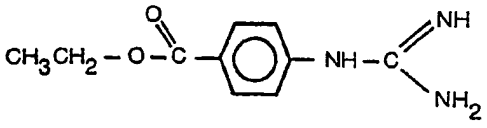
It is understood that the series of examples of aromatic diamidines in Table I, below will also exemplify the aromatic diguanidines in every respect except that for the latter class of compounds guanidino groups:



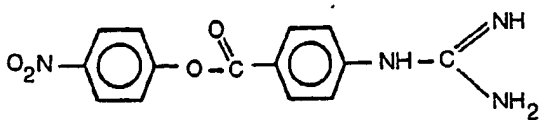
are substituted for amidino groups:



Two examples of aromatic monoguanidines are the following

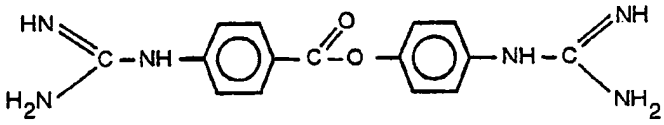


ethyl-p-guanidinobenzoate and

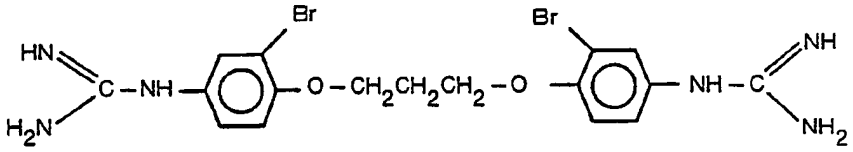


p-nitrophenyl-p'-gunaidinobenzoate (commonly named NPGB).

Two examples of aromatic diguanidines are the following:

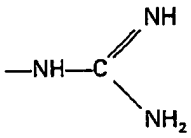


P-guanidinophenyl-p'-guanidinobenzoate and

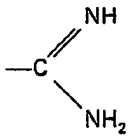


1,3-bis(2-bromo-4-guanidinophenoxy)propane.

{This last compound is analogous to dibromopropamidine (Table I) except that it is a diguanidine rather than a diamidine by virtue of the two guanidino groups:

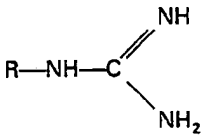


at both extremities of the molecule in place of the two amidino groups:



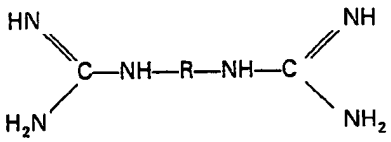
This diguanidine is assigned a chemical name in this application rather than a common or trivial name (such as "dibromopropaguanidine") because the compound and its analogs are not in common use and have not been previously given common names in the scientific literature.}.

The non-aromatic guanidines may be a non-aromatic monoguanidine of the general formula:



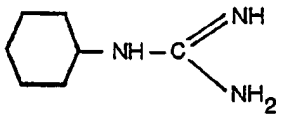
wherein R may represent a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfur, etc.); a cyclic non-aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination.

As preferred for utilization in the invention herein, there may be utilized a non-aromatic diguanidine of the general formula:



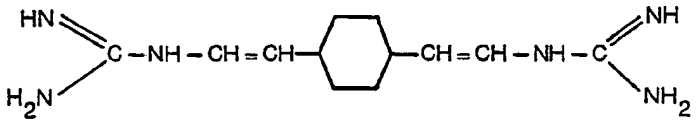
R may represent a carbon chain with or without other elements (such as hydrogen, nitrogen, oxygen, sulfur, etc.); a cyclic aromatic group (such as cyclohexane) with or without additional carbons, carbon chains, and other elements; or any of the above in combination.

An example of a non-aromatic monoguanidine is the following:



guanidinocyclohexane.

An example of a non-aromatic diguanidine is the following:



1,4-di(2-guanidinovinyl)cyclohexane.

In the above,

represents cyclohexane.

TABLE I

AROMATIC DIAMIDINES

Drug Name	R_1.Carbon Chain	R_2	R_3	Relative Potency
Dibromopropamidine	C_3H_6	Br	Br	1.0
Phenamidine	—	H	H	0.2
Octamidine	C_8H_{16}	H	H	2.6
m-Pentamidine	C_5H_{10}	H	H	0.6
Hexamidine	C_6H_{12}	H	H	1.6
Dichlorohexamidine	C_6H_{12}	Cl	Cl	1.9
Pentamidine	C_5H_{10}	H	H	2.4
Monoiodohexamidine	C_6H_{12}	I	H	4.4
Dibromopentamidine	C_5H_{10}	Br	Br	3.6
Propamidine	C_3H_6	H	H	1.2
Heptamidine	C_7H_{14}	H	H	1.9
Diiodopentamidine	C_5H_{10}	I	I	6.8
Diiodohexamidine	C_6H_{12}	I	I	7.5
Budamidine	C_4H_8	H	H	
Monochloropropamidine	C_3H_6	Cl	H	

TABLE I (Continued)

AROMATIC DIAMIDINES

Drug Name	R_1 Carbon Chain	R_2	R_3	Relative Potency
Monochlorobutamidine	C_4H_8	Cl	H	
Monochloropentamidine	C_5H_{10}	Cl	H	
Monochlorohexamidine	C_6H_{12}	Cl	H	
Monochloroheptamidine	C_7H_{14}	Cl	H	
Monochloroctamidine	C_8H_{16}	Cl	H	
Monochlorononamidine	C_9H_{18}	Cl	H	
Monobromopropamidine	C_3H_6	Br	H	
Monobromofutamidine	C_4H_8	Br	H	
Monobromopentamidine	C_5H_{10}	Br	H	
Monobromohexamidine	C_6H_{12}	Br	H	
Monobromoheptamidine	C_7H_{14}	Br	H	
Monobromoctamidine	C_8H_{16}	Br	H	
Monobromononamidine	C_9H_{18}	Br	H	
Monoiodopropamidine	C_3H_6	I	H	
Monoiodobutamidine	C_4H_6	I	H	
Monoiodopentamidine	C_5H_{10}	I	H	
Monoiodohexamidine	C_6H_{12}	I	H	
Monoiodoheptamidine	C_7H_{14}	I	H	
Monoiodoctamidine	C_8H_{16}	I	H	
Monoiodononamidine	C_9H_{18}	I	H	
Dichloropropamidine	C_3H_6	Cl	Cl	
Dichlorobutamidine	C_4H_8	Cl	Cl	
Dichloropentamidine	C_5H_{10}	Cl	Cl	
Dichlorohexamidine	C_6H_{12}	Cl	Cl	
Dichloroheptamidine	C_7H_{14}	Cl	Cl	
Dichloroctamidine	C_5H_{16}	Cl	Cl	
Dichlorononamidine	C_9H_{19}	Cl	Cl	
Dibromopropamidine (already listed)	C_3H_6	Br	Br	
Dibromobutamidine	C_4H_8	Br	Br	

TABLE I (Continued)

AROMATIC DIAMIDINES

Drug Name	R_1 Carbon Chain	R_2	R_3	Relative Potency
Dibromopentamidine	C_5H_{10}	Br	Br	
Dibromohexamidine	C_6H_{12}	Br	Br	
Dibromoheptamidine	C_7H_{14}	Br	Br	
Dibromoctamidine	C_8H_{16}	Br	Br	
Dibromononamidine	C_9H_{18}	Br	Br	
Diiodopropamidine	C_3H_6	I	I	
Diiodobutamidine	C_4H_8	I	I	
Diiodopentamidine	C_5H_{10}	I	I	
Diiodohexamidine	C_6H_{12}	I	I	
Diiodoheptamidine	C_7H_{14}	I	I	
Diiodooctamidine	C_8H_{16}	I	I	
Diiodononamidine	C_9H_{18}	I	I	
Monochloromonobromopropamidine	C_3H_6	Cl	Br	
Monochloromonobromobutamidine	C_4H_8	Cl	Br	
Monochloromonobromopentamidine	C_5H_{10}	Cl	Br	
Monochloromonobromohexamidine	C_6H_{12}	Cl	Br	
Monochloromonobromoheptamidine	C_7H_{14}	Cl	Br	
Monochloromonobromooctamidine	C_8H_{16}	Cl	Br	
Monochloromonobromononamidine	C_9H_{18}	Cl	Br	
Monochloromonoiodopropamidine	C_3H_6	Cl	I	
Monochloromonoiodobutamidine	C_4H_8	Cl	I	
Monochloromonoidopentamidine	C_5H_{10}	Cl	I	
Monochloromonoiodohexamidine	C_6H_{12}	Cl	I	
Monochloromonoiidoheptamidine	C_7H_{14}	Cl	I	
Monochloromonoiodooctamidine	C_8H_{16}	Cl	I	
Monochloromonoiodononamidine	C_9H_{18}	Cl	I	
Monobromomonoiodopropamidine	C_3H_6	Br	I	
Monobromomonoiodobutamidine	C_4H_8	Br	I	
Monobromomonoiodopentamidine	C_5H_{10}	Br	I	

TABLE I (Continued)

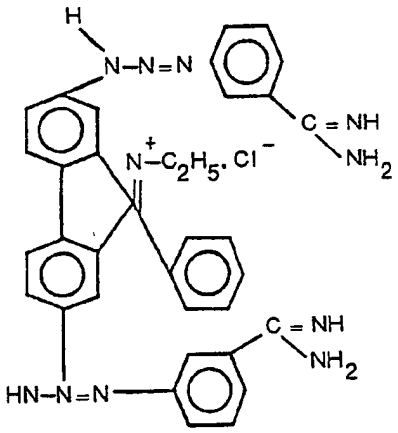
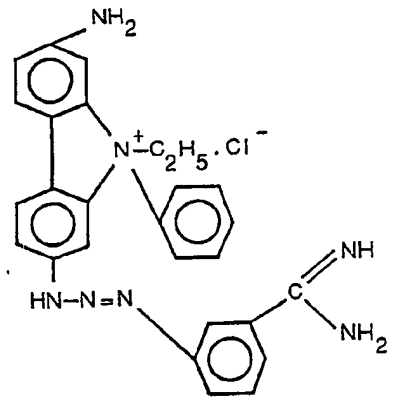
AROMATIC DIAMIDINES

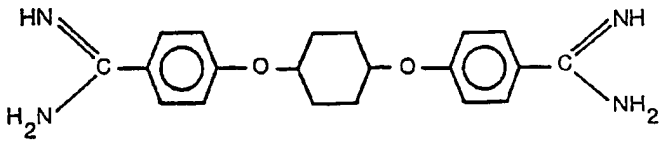
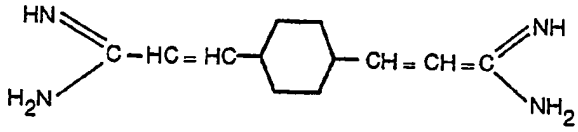
Drug Name	R_1 Carbon Chain	R_2	R_3	Relative Potency
Monobromomonoiodohexamidine	C_6H_{12}	Br	I	
Monobromomonoiodoheptamidine	C_7H_{14}	Br	I	
Monobromomonoiodooctamidine	C_8H_{16}	Br	I	
Monobromomonoiodononamidine	C_9H_{18}	Br	I	

In addition to the specified aromatic diamidines listed in Table I, other aromatic diamidines, aromatic monomidines and non-aromatic diamidines may also be utilized in accordance with the principles of the present invention.

Further, in addition to the aromatic diguanidines, which, as noted above, are similar to the aromatic diamidines listed in Table I except for the substitution of the guanidine group for the amidine group in the drug and which, when trivial names have been assigned thereto will have trivial names similar to those shown in Table I other aromatic diguanidines, aromatic monoguanidines, non-aromatic monoguanidines and non-aromatic diguanidines may also be utilized in accordance with the principles of the present invention.

Further, it has been found that the following compounds are also useful in the practice of the present invention:

DRUG	SPECIFIC FORMULA
3,8-Di(*m*-amidinophenyldiazoamino)-5-ethyl-6-phenylphenanthridinium chloride dihydrochloride hydrate (aromatic diamidine)	
8-(m-amidophenyldiazoamino)-3-amino-5-ethyl-6-phenylphenanthridinium chloride (aromatic monoamidine)	

DRUG	SPECIFIC FORMULA
1,4-di(p-amidinophenoxy) cyclohexane (aromatic diamidine)	
1,4-di(2-amidinovinyl) cyclohexane (nonaromatic diamidine)	

The relative potency shown in Table 1 is expressed in relationship to dibromopropamidine, which has been discovered to be a highly potent fibrinolytic inhibitor. The numerical values are expressed as a reciprocal of the concentration of the drug producing the equivalent inhibition to the dibromopropamidine. Where no values for relative potency are listed such values have not been specifically determined.

The exact relative potency for the guanidines of the present invention has not yet been completely determined. However those skilled in the art may rapidly determine the relative potency for any particular guanidine selected.

Referring now to the drawing, there are illustrated in Figures 1 through 5 thereof various well-known forms of intrauterine devices heretofore utilized. According to the principles of the present invention, many of the forms shown in Figures 1 through 5, as well as any other geometrical configurations of intrauterine devices, may be utilized in the practice of the present invention. Thus, the illustration of the known intrauterine devices illustrated in Figures 1 through 5 herein is not limiting to the principles of the present invention.

In the intrauterine devices shown in Figures 1 through 5, as well as in other configurations, the IUDs are generally comprised of a body member 8 of a polymer matrix having a relatively thick structural portion 10 and may or may not, as desired, be provided with one or more comparatively thin leaves 12. According to the principles of the present invention, in one embodiment thereof, the drug, which as noted above, may be one or more of ghe guanidines, or one or more guanidines mixed with one or more of the amidines, is mixed with the polymer matrix of the body member 8 in a predetermined ratio, depending upon the desired concentration of the drug within the uterus. The polymer of the body member 8 may be, for example:

1. low density polyethylene, or,
2. polyethyl vinyl acetate.

The ratio may be, for example, on the order of 10% to 50% by weight of the body member 8, depending upon the potency of the drug and the particular polymer matrix of the body member 8. Additionally, the shape, charge, and other characteristics of the drug molecule, such as its hydrophobicity, as well as similar characteristics of the polymer matrix, may be varied as desired to select the particular release rate of the drug from the body member 8 when placed within the uterus.

In another embodiment of the present invention, the drug may be provided as a biodegradable polymer or copolymer and mixed in the supporting polymer matrix of the body member 8 with selection of characteristics as above defined.

In another embodiment of the present invention, the drug is provided in a biodegradable polymer or copolymer form and it is covalently bonded to the polymer matrix of the body member 8 either or both within the body member 8 or on the surface thereof.

In any of the embodiments described above, there may also be provided, in another embodiment of the present invention, a biodegradable cross-linked polymer or copolymer coating of the drug bonded covalently to the surface of the polymer matrix of the body member 8 in order to provide a soft hydrogel coating thereof. Such a coating is likely to be particularly effective in aiding retention of the intrauterine device in the uterus during the time period soon after insertion thereof. The coating may be provided for some or all of the surface of the body member 8.

In another embodiment of the present invention, the drug is provided in a non-biodegradable monomer, dimer, or oligomer or a cross-linked polymer on the outer surface of the polymer matrix of the body member 8. This coating may be provided by covalent or other chemical bonding between drug molecules and the surface of the body member polymer matrix. Since the bleeding of the endometrium is at the interface between the endometrium and the intrauterine device, the solid phase enzyme inhibition provided by the drug at the point of contact between the endometrium and the intrauterine device can reduce the bleeding associated with utilizing an intrauterine device. In addition, the predetermined release of drug from the body member 8 will occur.

Further, since copper release has also been proven anti-conceptive in IUDs, some of the surface of the body member 8 may be provided with a coating of metallic copper such as wire, plating or the like. However, of course, such coating of metallic copper should not completely cover the body member 8 since that would prevent drug release.

It has been found that the drugs according to the present invention may provide an anti-conceptive effect. It is believed that this effect, which should enhance the anti-conceptive effect of the intrauterine device itself, is due to the activity of the drug and its action on the very early embryo and possibly on the sperm.

Further, it is believed yet an additional unexpected and surprising result may be obtained due to the anti-proteolytic action of the drug. This effect is a reduction in the pain and/or cramps and expulsion heretofore associated with utilization of intrauterine devices including medicated IUDs.

The range of concentrations necessary to provide the desired effects mentioned above depend, of course, upon the particular drug or combinations selected. For example, for dibromopropamidine introduced into the uterine cavity and endomatrial tissue water, and with an endometrial water turnover rate of 200 milliliters per day and with complete distribution of the drug in the endometrial water turned over, an intrauterine release rate of 50 to 200 μg per day would be expected to produce a concentration of dibromopropamidine in the range of 0.5 to 2.0 x 10^{-6} moles per litre in endometrial water. Since, in general, there will be less than complete distribution of the drug into the endometrial water turned over each day, the concentration of the drug in the uterine cavity could reach much higher levels; for example, on the order of 10^{-6} to 10^{-4} moles per litre. This concentration range is sufficient to provide both the anti-fibrinolytic effects, as well as the anti-conceptive or anti-fertility effects desired, and also, it is believed, the reduction in pain, cramps and expulsion. With the above release rate (50—200 μg per day), the known sizes of intrauterine devices currently available, and the amount of drug which can be incorporated into such devices, an effective life span of, for example, one to three years can be provided for such medicated devices.

At least one aromatic guanidine, NPGB as identified above, has an anti-fibrinolytic effect on the order of 100 times greater than that of dibromopropamidine (on a molar concentration basis). As little as 0.5 μg to 2.0 μg per day release of NPGB from a medicated IUD according to the principles of the present invention may be satisfactorily effective. Thus, the estimated range of daily release of the drug according to the present invention from a medicated IUD may be as low as, for example, 0.5 μg to as high as 200 μg, depending upon the particular constituents selected for inclusion in the drug. The useful life span of a device releasing, for example, 0.5 μg per day may greatly exceed three years.

Those skilled in the art, of course, can readily determin the appropriate release rate desired for any drug or combination thereof which may be utilized according the present invention and, in accordance with known principles, establish the desired release rate thereof to achieve effectiveness.

In those embodiments of the present invention wherein a drug is provided as a coating on the surface of the IUD, the body member of the IUD may also incorporate a drug according to the principles of the present invention mixed therewith or the drug may be provided only in the coating. In those embodiments wherein a drug is provided as a coating on the surface of the IUD and a drug is also incorporated in the body member, the drug of the coating may be the same as the drug in the body member or they may be different drugs.

Medicated intra-uterine devices wherein the medicament is a guanidine or amidine are described and claimed in my copending Eurpean Patent Application No. 80 300 257 (EP—A—24779).

Claims

1. A medicated intrauterine device of the type insertable in the uterus said device having a controlled rate of release of said medicament and comprising a body member at least a portion of which comprises a polymer matrix incorporating said medicament characterized in that the medicament is a drug comprising an amidine and/or a guanidine or an ester of salt thereof which is capable of exhibiting an anti-proteolytic, an anti-fibrinolytic and anti-conceptive effect when released at said controlled rate.

2. The device defined in Claim 1 wherein the controlled rate is 50 to 200 μg per day.

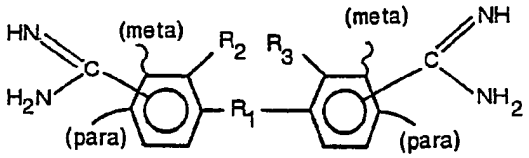
3. The device in Claim 1 wherein said drug comprises:

(a) an amidine;
(b) a mixture of an amidine and a guanidine;
(c) a mixture of more than one amidine and a guanidine;
(d) a mixture of an amidine and more than one guanidine;
(e) a mixture of more than one amidine and more than one guanidine;
(f) a guanidine; and
(g) a mixture of more than one guanidine.

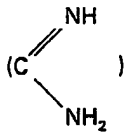
4. The device defined in any of claims 1 to 3 in which the amidine is an aromatic monoamidine, aromatic diamidine or an non-aromatic diamidine.

5. The device defined in any of claims 1 to 3 wherein:

said drug is selected from the class consisting of aromatic diamidines of the group



in which each amidine group



may be substituted in either a meta or para position with respect to R_1.

R_1 is selected from the group consisting of C_xH_y; and

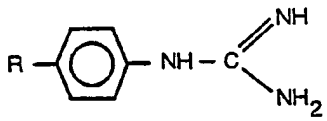
R_2 and R_3 are selected from the group consisting of hydrogen, chlorine, bromine, iodine, hydroxyl group and alkyl groups; and

represents the benzene ring.

6. The device defined in any one of Claims 1 to 3 wherein:
said drug is selected from the class consisting of:
3,8-Di(*m*-amidinophenyldiazoamino)-5-ethyl-6-phenylphenanthridinium chloride dihydrochloride hydrate 8-m(m-Amiophenyldiazoamino)-3-amino-5-ethyl-6-phenylphenanthridinium chloride,
1,4-di(p-amidinophenoxy) cyclohexane, and
1,4-di(2-amidinovinyl)cyclohexane.

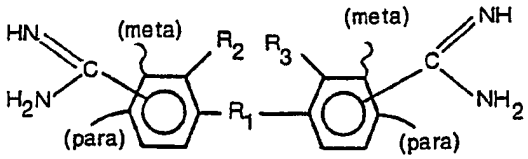
7. The device defined in any of claims 1 to 3 wherein:
said guanidine of said at least one drug is selected from the class consisting of:
(a) aromatic monoguanidines;
(b) aromatic diguanidines;
(c) non-aromatic monoguanidines; and
(d) non-aromatic diguanidines.

8. The device defined in any one of Claims 1 to 3 wherein:
at least one drug is selected from aromatic monoguanidines of the group:

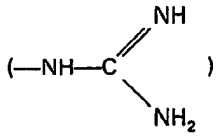


wherein R is
(a) a carbon chain free of other elements;
(b) a carbon chain with at least one other element;
(c) an aromatic group free of additional carbon atoms, carbon chains and other elements;
(d) an aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;
(e) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;
(f) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains, and other elements; and
(g) a combination of at least two of (a), (b), (c), (d), (e) and (f); and
wherein:

represents the benzene ring and/or at least one drug is selected from the class of aromatic diguanidines of the group;



and wherein each guanidine group



is in one of a meta or para position with respect to R_1, and in which:

R_1 is

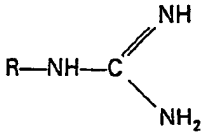
(a) a hydrocarbon chain free of ether and ester bonds to the benzene ring; and

(b) a hydrocarbon chain having at least one bond selected from the class of ether bonds and ester bonds to the benzene ring;

R_2 and R_3 are

hydrogen, chlorine, bromine, iodine, hydroxyl group and alkyl group; and

represents the benzene ring, and/or at least one drug is selected from the class of non-aromatic mono-guanidines of the group:



wherein R is

(a) a carbon chain free of other elements;

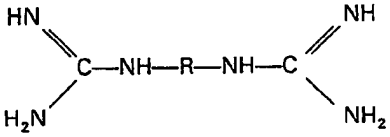
(b) a carbon chain with at least one other element;

(c) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;

(d) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;

(e) a combination of at least two of (a), (b), (c), and (d); and/or

at least one drug is a non-aromatic diguanidine of the group:



wherein R is

(a) a carbon chain free of other elements;

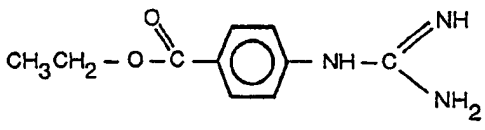
(b) a carbon chain with at least one other element;

(c) a cyclic non-aromatic group free of additional carbon atoms, carbon chains and other elements;

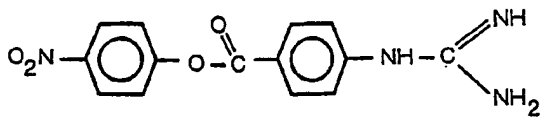
(d) a cyclic non-aromatic group with at least one addition selected from the class consisting of carbon atoms, carbon chains and other elements;

(e) a combination of at least two of (a), (b), (c), and (d); and/or

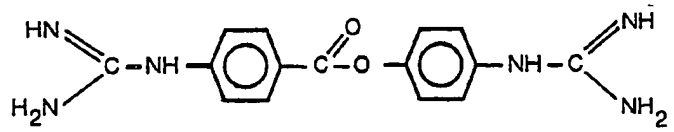
at least one drug is



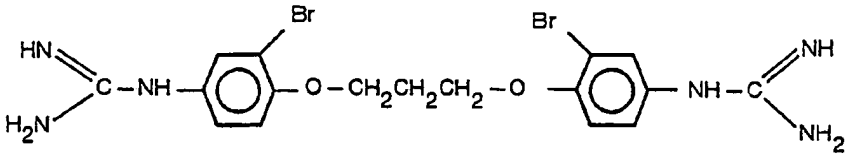
ethyl-p-guanidinobenzoate,



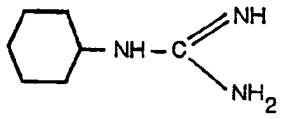
p-nitrophenyl-p'-guanidinobenzoate (commonly named NPGB),



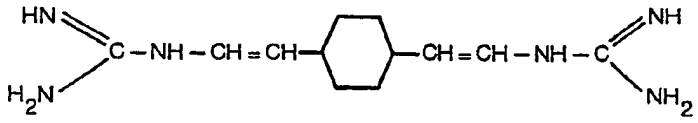
p-guanidinophenyl-p'-guanidinobenzoate,



1,3-bis(2-bromo-4-guanidinophenoxy)propane,



guanidinocyclohexane, and/or



1,4-di(2-guanidinovinyl)cyclohexane.

9. The device defined in any one of the preceding claims wherein:

said body member further comprises a structural portion having a second predetermined thickness less than said first determined thickness and extending between preselected sections of said structural portion.

10. The device defined in any one of the preceding claims wherein:

said body member comprises a polymer matrix having a predetermined geometrical configuration and said at least one drug is mixed in said polymer matrix.

11..The device defined in any one of claims 1 to 9 wherein:

said body member comprises a polymer matrix having a predetermined geometrical configuration and said at least one drug is in at least one of a biodegradable polymer and copolymer form and is mixed with said polymer matrix.

12. The device defined in any one of claims 1 to 9 wherein:

Said body member comprises a polymer matrix having a predetermined geometrical configuration and said at least one drug is in one of a biodegradable polymer and copolymer form and is chemically bonded to said polymer matrix.

13. The device defined in Claim 12 wherein:

said chemical bonding is on at least some of the surface of said polymer matrix and is covalent bonding.

14. The device defined in any one of claims 1 to 13 and further comprising:

a coating on the surface of said body member comprising one of biodegradable cross-linked polymer and copolymer form of a drug selected from the same group as said at least one drug, and hard coating covalently bonded to at least some of the surface of said polymer matrix.

15. The device defined in any one of claims 1 to 13 and further comprising:

A coating on a first portion of said external surface of said body member comprising one of a

biodegradable cross-linked polymer and biodegradable cross-linked copolymer form of a second drug, and said second drug comprising at least a guanidine, and said second drug being covalently bonded to said surface of said polymer matrix.

16. The device defined in any one of the preceding claims and further comprising:

a coating on at least some of the surface of said polymer matrix, and said coating comprising one of a non-biodegradable monomer, dimer, oligomer, and cross-linked polymer form of a drug selected from the same group as said at least one drug.

17. The device defined in any one of the preceding claims and further comprising:

a coating of copper on a portion of the external surface of said body member.

18. The device defined in any one of claims 1 to 17 wherein said at least one drug comprises a soft hydrogel coating on a first portion of said external surface of said body member, and said at least one drug is in the form of one of a biodegradable cross-linked polymer and biodegradable copolymer covalently bonded to said body member.

Revendications

1. Dispositif intra-utérin médicamenté du type pouvant être inséré dans l'utérus, ledit dispositif ayant une vitesse réglée de libération dudit médicament et comportant un corps dont une partie au moins comprend une matrice de polymère renfermant ledit médicament, caractérisé en ce que le médicament est une substance médicinale comprenant une amidine et/ou une guanidine ou un ester ou un sel correspondant qui est capable de produire un effet anti-protéolytique, un effet antifibrinolytique et un effet contraceptif lorsqu'il est libéré à ladite vitesse réglée.

2. Dispositif suivant la revendication 1, pour lequel la vitesse réglée est de 50 à 200 μg par jour.

3. Dispositif suivant la revendication 1, dans lequel ladite substance médicinale comprend:

(a) une amidine;

(b) un mélange d'une amidine et d'une guanidine;

(c) un mélange de plus d'une amidine et d'une guanidine;

(d) un mélange d'une amidine et de plus d'une guanidine;

(e) un mélange de plus d'une amidine et de plus d'une guanidine;

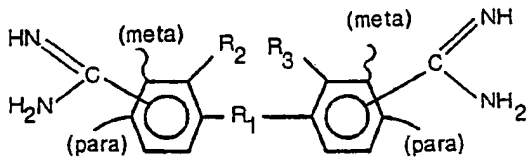
(f) une guanidine; et

(g) un mélange de plus d'une guanidine.

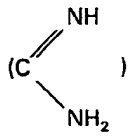
4. Dispositif suivant l'une quelconque des revendications 1 à 3, dans lequel l'amidine est une monoamidine aromatique, une diamidine aromatique ou une diamidine non aromatique.

5. Dispositif suivant l'une quelconque des revendications 1 à 3 dans lequel:

ladite substance médicinale est choisie dans la classe comprenant des diamidines aromatiques du groupe



dans lequel chaque groupe amidino



peut être substitué dans une position méta ou para par rapport à R_1

R_1 est choisi dans le groupe formé de C_xH_y; et

R_2 et R_3 sont choisis dans le groupe comprenant l'hydrogène, le chlore, le brome, l'iode, le groupe hydroxyle et des groupes alkyle; et

représente le noyau benzénique.

6. Dispositif suivant l'une quelconque des revendications 1 à 3 dans lequel:

ladite substance médicinale est choisie dans la classe comprenant:

le dichlorhydrate de chlorure de 3,8-di(m-amidinophényldiazoamino)-5-éthyl-6-phényl-phénanthridinium hydraté,

le chlorure de 8-(m-amidiophényldiazoamino)-3-amino-5-éthyl-6-phénylphénanthridinium,
le 1,4-di(p-amidinophénoxy)cyclohexane, et
le 1,4-di(2-amidinovinyl)cyclohexane.

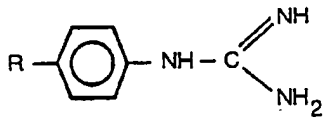
7. Dispositif suivant l'une quelconque des revendications 1 à 3, dans lequel:

ladite guanidine de ladite substance médicinale dont au moins une est présente, est choisie dans la classe comprenant:

(a) des monoguanidines aromatiques;
(b) des diguanidines aromatiques;
(c) des monoguanidines non aromatiques; et
(d) des diguanidines non aromatiques.

8. Dispositif suivant l'une quelconque des revendications 1 à 3, dans lequel

au moins une substance médicinale est choisie entre des monoguanidines aromatiques de formule:



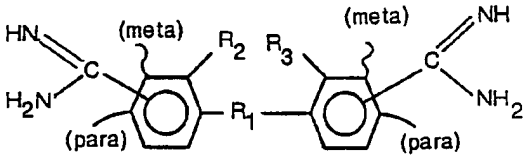
dans laquelle R représente

(a) une chaîne carbonée dépourvue d'autres éléments;
(b) une chaîne carbonée avec au moins un autre élément;
(c) un groupe aromatique dépourvu d'atomes additionnels de carbone, de chaînes carbonées et d'autres éléments;
(d) un groupe aromatique présentant au moins une addition choisie dans la classe comprenant des atomes de carbone, des chaînes carbonées et d'autres éléments;
(e) un groupe cyclique non aromatique dépourvu d'atomes additionnels de carbone, de chaînes carbonées et d'autres éléments;
(f) un groupe cyclique non aromatique présentant au moins une addition choisie dans la classe comprenant des atomes de carbone, des chaînes carbonées et d'autres éléments et
(g) une association d'au moins deux des options (a), (b), (c), (d), (e) et (f); et

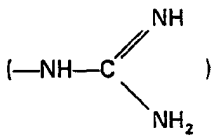
dans lequel:

représente le noyau benzénique;

et/ou au moins une substance médicinale est choisie dans la classe des diguanidines aromatiques du groupe:



et dans lequel chaque groupe guanidino



occupe une position méta ou para par rapport à R_1, et dans lequel:

R_1 représente

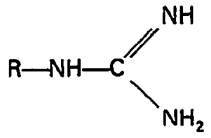
(a) une chaîne hydrocarbonée dépourvue de liaisons éther et ester avec le noyau benzénique; et

(b) une chaîne hydrocarbonée ayant au moins une liaison choisie dans la classe des liaisons éther et des liaisons ester avec le noyau benzénique;

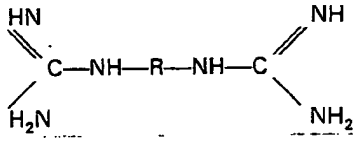
R_2 et R_3 sont

de l'hydrogène, du chlore, du brome, de l'iode, un groupe hydroxyle et un groupe alkyle; et

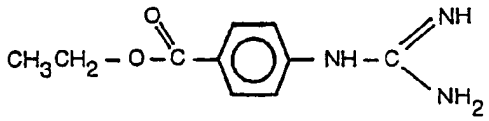
représente le noyau benzénique;
et/ou moins une substance médicinale choisie dans la classe des monoguanidines non aromatiques du groupe:



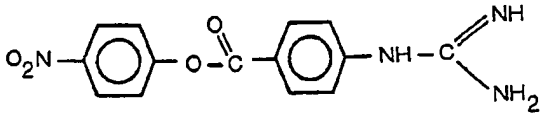
dans lequel R représente
(a) une chaîne carbonée dépourvue d'autres éléments;
(b) une chaîne carbonée avec au moins un autre élément;
(c) un groupe cyclique non aromatique dépourvu d'atomes additionels de carbone, de chaînes carbonées et d'autres éléments;
(d) un groupe cyclique non aromatique présentant au moins une addition choisie dans la classe comprenant des atomes de carbone, des chaînes carbonées et d'autres éléments;
(e) une association d'au moins deux des options (a), (b), (c), et (d); et/ou
au moins une substance médicinale est une diguanidine non aromatique du groupe:



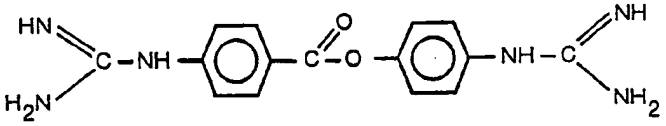
dans lequel R représente
(a) une chaîne carbonée dépourvue d'autres éléments;
(b) une chaîne carbonée avec au moins un autre élément;
(c) un groupe cyclique non aromatique dépourvu d'atomes additionnels de carbone, de chaînes carbonées et d'autres éléments;
(d) un groupe cyclique non aromatique présentant au moins une addition choisie dans la classe comprenant des atomes de carbone, des chaînes carbonées et d'autres éléments;
(e) une association d'au moins deux des options (a), (b), (c), et (d); et/ou
au moins une substance médicinale représente:



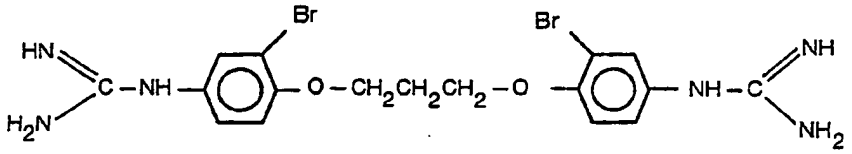
p-guanidinobenzoate d'éthyle,



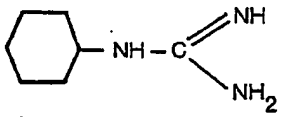
p'-guanidinobenzoate de p-nitrophényle (communément appelé NPGB),



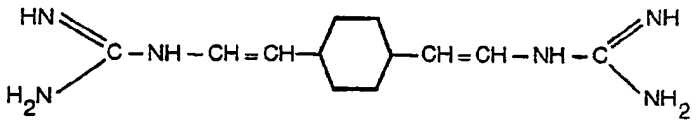
p'-guanidinobenzate de p-guanidinophényle,



1,3-bis(2-bromo-4-guanidinophénoxy)propane,



guanidinocyclhexane, et/ou



1,4-di(2-guanidinovinyl)cyclohexane.

9. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel:

ledit corps comprend en outre une partie structurale ayant une première épaisseur prédéterminée et une partie en feuille ayant une seconde épaisseur prédéterminée inférieure à la première épaisseur prédéterminée et s'étendant entre des portions préalablement choisies de ladite partie structurale.

10. Dispositif suivant l'une quelconque des revendications précédentes, dans lequel:

ledit corps comprend une matrice en polymère ayant une configuration géométrique prédéterminée et ladite substance médicinale dont au moins une est présente est incorporée à ladite matrice de polymère.

11. Dispositif suivant l'une quelconque des revendications 1 à 9, dans lequel

ledit corps comprend une matrice en polymère à configuration géométrique prédéterminée et ladite substance médicinale, dont au moins une est présente, se trouve sous au moins l'une des formes d'un polymère et d'un copolymère biodégradables et est en mélange avec ladite matrice de polymère.

12. Dispositif suivant l'une quelconque des revendications 1 à 9, dans lequel:

ledit corps comprend une matrice en polymère à configuration géométrique prédéterminée et ladite substance médicinale dont au moins une est présente est sous l'une des formes d'un polymère et d'un copolymère biodégradables et est chimiquement liée à ladite matrice en polymère.

13. Dispositif suivant la revendication 12, dans lequel:

ladite liaison chimique s'effectue sur au moins une partie de la surface de ladite matrice en polymère et est une liaison de covalence.

14. Dispositif suivant l'une quelconque des revendications 1 à 13, et comprenant en outre:

un revêtement à la surface dudit corps comprenant l'une des formes de polymère et de copolymère réticulés biodégradables d'une substance médicinale choisie dans le même groupe que ladite substance médicinale dont au moins une est présente, et un revêtement dur en liaison de covalence avec au moins une partie de la surface de ladite matrice en polymère.

15. Dispositif suivant l'une quelconque des revendjcations 1 à 13 et comprenant en outre:

un revêtement sur une première partie de ladite surface externe dudit corps, comprenant l'une des formes de polymère réticulé biodégradable et de copolymère réticulé biodégradable d'une seconde substance médicinale, et ladite seconde substance médicinale comprend au moins une guanidine et étant en liaison de covalence avec ladite surface de ladite matrice en polymère.

16. Dispositif suivant l'une quelconque des revendications précédentes et comprenant en outre:

un revêtement sur au moins une partie de la surface de ladite matrice en polymère et ledite revêtement comprenant l'une des formes de monomère, de dimère d'oligomère et de polymère réticulé non biodégradables d'une susbtance médicinale choisie dans le même groupe que ladite substance médicinale dont au moins une est présente.

17. Dispositif suivant l'une quelconque des revendications précédentes, comprenant en outre:

un revêtement de cuivre sur une partie de la surface externe dudit corps.

18. Dispositif suivant l'une quelconque des revendications 1 à 17, dans lequel ladite substance médicinale dont au moins une est présente comprend un revêtement d'hydrogel mou sur une première partie de ladite surface externe dudit corps et la substance médicinale dont au moins une est présente est sous la forme d'un polymère réticulé biodégradable ou d'un copolymère biodégradable en liaison de covalence avec ledit corps.

Patentansprüche

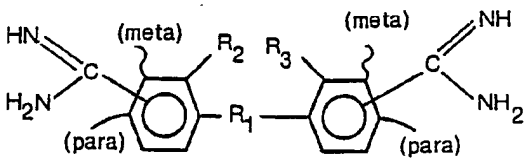
1. Eine ein Medikament aufweisende intra-uterine Vorrichtung vom in den Uterus einsetzbaren Typ, welche Vorrichtung eine kontrollierte Geschwindigkeit der Freisetzung des Medikaments aufweist und die einen Grundkörper umfaßt, der zumindest teilweise eine Polymermatrix enthält, in die das Medikament einverleibt ist, dadurch gekennzeichnet, daß das Medikament ein Arzneimittel ist, das ein Amid und/oder ein Guanidin oder ein Ester oder ein Salz desselben umfaßt, das in der Lage ist, eine antiproteolytische, antifibrinolytische und antikonzeptive Wirkung zu zeigen, wenn es mit der kontrollierten Geschwindigkeit freigesetzt wird.

2. Vorrichtung nach Anspruch 1, wobei die kontrollierte Geschwindigkeit 50 bis 200 μg pro Tag beträgt.

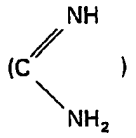
3. Vorrichtung nach Anspruch 1, wobei das Arzneimittel
(a) ein Amidin;
(b) ein Gemisch aus einem Amidin und einem Guanidin;
(c) ein Gemisch aus mehr als einem Amidin und einem Guanidin;
(d) ein Gemisch aus einem Amidin und mehr als einem Guanidin;
(e) ein Gemisch aus mehr als einem Guanidin und mehr als einem Amidin;
(f) ein Guanidin; und
(g) ein Gemisch aus mehr als einem Guanidin umfaßt.

4. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der das Amidin ein aromatisches Monoamidin, aromatisches Diamidin oder ein nichtaromatisches Diamidin ist.

5. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der das Arzneimittel ausgewählt wird aus einer Klasse, die aus aromatischen Diaminen der Gruppe



besteht, wobei jede Amidingruppe



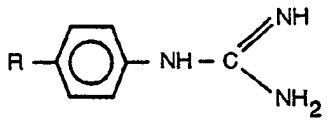
entweder in einer Meta- oder in einer Para- position gegenüber R_1 substituiert sein kann, wobei
R_1 aus einer Gruppe ausgewählt wird, die aus C_xH_y besteht; und
R_2 und R_3 aus einer Gruppe ausgewählt werden, die aus Wasserstoff, Chlor, Brom, Jod, einer Hydroxylgruppe und Alkylgruppen besteht; und

einen Benzolring darstellt.

6. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der das Arzneimittel aus einer Klasse ausgewählt wird, die besteht aus
3,8-De(*m*-amidinophenyldiazoamino)-5-ethyl-6-phenylphenanthridinium-chlorid-Dihydrochlorid-Hydrat 8-m(m-Aminophenyldiazoamino)-3-amino-5-ethyl-6-phenylphenanthridinium-chlorid,
1,4-Di(p-amidinophenoxy)-cyclohexan, und
1,4-Di(2-amidinovinyl)-cyclohexan.

7. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der das Guanidin des wenigstens einen Arzneimittels aus einer Klasse ausgewählt wird, die besteht aus
(a) aromatischen Monoguanidinen;
(b) aromatischen Diguanidinen;
(c) nichtaromatischen Monoguanidinen; und
(d) nichtaromatischen Diguanidinen.

8. Vorrichtung nach einem der Ansprüche 1 bis 3, bei der wenigstens eine der Arzneimittel ausgewählt wird aus aromatischen Monoguanidinen der Gruppe



worin R

(a) eine Kette von Kohlenstoffatomen ohne andere Elemente;

(b) eine Kohlenstoffatomkette mit wenigstens einem weiteren Element;

(c) eine aromatische Gruppe, die keine zusätzlichen Kohlenstoffatome, Kohlenstoffketten und andere Elemente aufweist;

(d) eine aromatische Gruppe mit wenigstens einem Substituenten, der aus einer Klasse ausgewählt wird, die aus Kohlenstoffatomen, Kohlenstoffketten und anderen Elementen besteht;

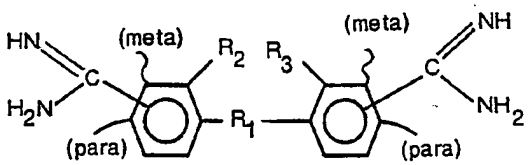
(e) eine zyklische nichtaromatische Gruppe, die keine weiteren Kohlenstoffatome, Kohlenstoffketten und andere Elemente aufweist;

(f) eine zyklische nichtaromatische Gruppe mit wenigstens einem Substituenten, der aus einer Klasse ausgewählt wird, die aus Kohlenstoffatomen, Kohlenstoffketten und anderen Elementen besteht; sowie

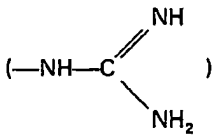
(g) eine Kombination von wenigstens zwei R aus (a), (b), (c), (d), (e) und (f) ist; und

worin

einen Benzolring darstellt und/oder wenigstens ein Arzneimittel aus einer Klasse ausgewählt wird, die aus aromatischen Diguanidinen der Gruppe



besteht, worin jede Guanidingruppe



einer Meta- oder Paraposition zu R_1 steht, und in der

R_1

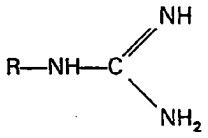
(a) eine Kohlenwasserstoffkette ohne Äther- und Esterbindungen an den Benzolring; und

(b) eine Kohlenwasserstoffkette mit wenigstens einer Bindung an de Benzolring, die aus einer Klasse ausgewählt wird, die aus Ätherbindungen und Esterbindungen besteht, ist; wobei

R_2 und R_3

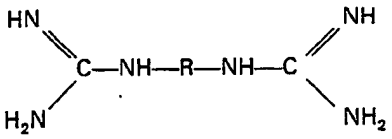
Wasserstoff, Chlor, Brom, Jod, eine Hydroxylgruppe und eine Alkylgruppe sind; und

einen Benzolring darstellt; und/oder wenigstens ein Arzneimittel ausgewählt wird aus einer Klasse von nichtaromatischen Monoguanidenen der Gruppe:

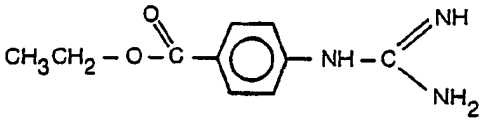


worin R

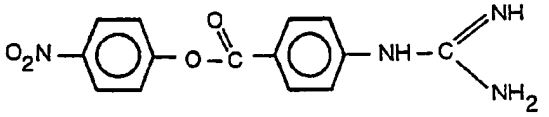
(a) eine Kohlenstoffkette ohne weitere Elemente;
(b) eine Kohlenstoffkette mit wenigstens einem weiteren Element;
(c) eine zyklische nichtaromatische Gruppe ohne zusätzliche Kohlenstoffatome, Kohlenstoffketten und andere Elemente;
(d) eine zyklische nichtaromatische Gruppe mit wenigstens einem Substituenten, der aus einer Klasse ausgewählt wird, die aus Kohlenstoffatomen, Kohlenstoffketten und anderen Elementen besteht; und
(e) eine Kombination von wenigstens zwei R aus (a), (b), (c) und (d) ist; und/oder wenigstens ein Arzneimittel ein nichtaromatisches Diguanidin der Gruppe



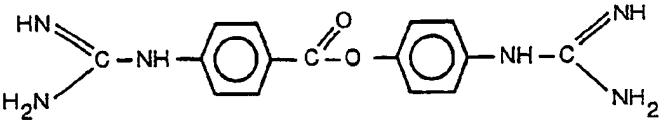
ist, worin R
(a) eine Kohlenstoffkette ohne weitere Elemente;
(b) eine Kohlenstoffkette mit wenigstens einem weiteren Element;
(c) eine zyklische nichtaromatische Gruppe ohne weitere Kohlenstoffatome, Kohlenstoffketten und andere Elemente;
(d) eine zyklishe nichtaromatische Gruppe mit wenigstens einem Substituenten, der aus einer Klasse ausgewählt wird, die aus Kohlenstoffatomen, Kohlenstoffketten und anderen Elementen besteht; und
(e) eine Kombination von wenigstens zwei R aus (a), (b), (c) und (d) ist; und/oder wenigstens ein Arzneimittel



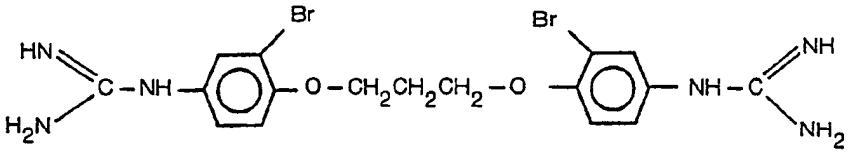
Ethyl-p-guanidinobenzoat,



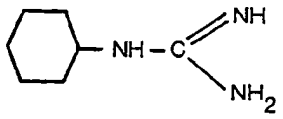
p-Nitrophenyl-p'-guanidinobenzoat, (bekannt als NPGB),



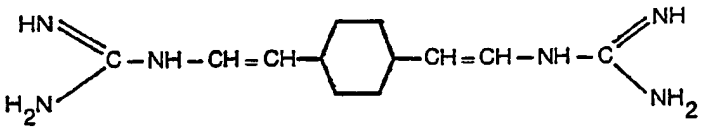
p-Guanidinophenyl-p'-guanidinobenzoat;



1,3-Bis(2-bromo-4-guanidinophenoxy)propan,



Guanidinocyclohexan, und/oder



1,4-Di(2-guanidinovinyl)cyclohexan ist.

9. Vorrichtung nach einem der vorstehenden Ansprüche, bei der der Grundkörper einen strukturellen Abschnitt aufweist, der eine erste vorgegebene Dicke sowie einen folienförmigen Abschnitt mit einer zweiten vorgegebenen Dicke aufweist, die geringer ist als die erste vorgegebene Dicke, welcher folienförmige Abschnitt sich zwischen vorgegebenen Bereichen des strukturellen Abschnitts erstreckt.

10. Vorrichtung nach einem der vorstehenden Ansprüche, bei der der Grundkörper eine Polymermatrix mit einer vorgegebenen geometrischen Konfiguration umfaßt, wobei wenigstens ein Arzneimittel in die Polymermatrix eingemischt ist.

11. Vorrichtung nach einem der Ansprüche 1 bis 9, bei der der Grundkörper eine Polymermatrix mit einer vorgegebenen geometrischen Konfiguration umfaßt, wobei wenigstens ein Arzneimittel in wenigstens einer biologisch abbaubaren Polymer- und Copolymerform vorliegt und in die Polymermatrix eingemischt ist.

12. Vorrichtung nach einem der Ansprüche 1 bis 9, wobei der Grundkörper eine Polymermatrix mit wenigstens einer vorgegebenen geometrischen Konfiguration umfaßt und das eine Arzneimittel in einer biologisch abbaubaren Polymer- und Copolymerform vorliegt und an die Polymermatrix chemisch gebunden ist.

13. Vorrichtung nach Anspruch 12, bei dme die chemische Bindung auf wenigstens einem Teil der Oberfläche der Polymermatrix vorliegt und eine kovalente Bindung ist.

14. Vorrichtung nach einem der Ansprüche 1 bis 13, die außerdem eine Beschichtung auf der Oberfläche des Grundkörpers umfaßt, die eine biologisch abbaubare vernetzte Polymer- und Copolymerform eines Arzneimittels umfaßt, das aus der gleichen Gruppe wie das wenigstens eine Arzneimittel ausgewählt ist, ferner eine harte Beschichtung, die wenigstens an einem Teil der Oberfläche der Polymermatrix kovalent gebunden ist.

15. Vorrichtung nach einem der Ansprüche 1 bis 13, die weiterhin eine Beschichtung auf einem ersten Abschnitt der äußeren Oberfläche des Grundkörpers umfaßt, die eine biologisch abbaubare vernetzte Polymer- und biologisch abbaubare vernetzte Copolymerform eines zweiten Arzneimittels umfaßt, wobei das zweite Arzneimittel wenigstens ein Guanidin umfaßt und das zweite Arzneimittel kovalent an die Oberfläche der Polymermatrix gebunden ist.

16. Vorrichtung nach einem der vorstehenden Ansprüche, die ferner eine Beschichtung an wenigstens einem Teil der Oberfläche der Polymermatrix umfaßt, wobei die Beschichtung eine biologisch nicht abbaubare Monomer-, Dimer-, Oligomer- und vernetzte Polymerform eines Arzneimittels umfaßt, das aus der gleichen Gruppe wie das wenigstens eine Arzneimittel ausgewählt ist.

17. Vorrichtung nach einem der vorstehenden Ansprüche, die weiterhin eine Beschichtung aus Kupfer an einem Teil der äußeren Oberfläche des Grundkörpers aufweist.

18. Vorrichtung nach einem der Ansprüche 1 bis 17, wobei wenigstens das eine Arzneimittel eine weiche Hydrogelbeschichtung auf dem ersten Abschnitt der äußeren Oberfläche des Grundkörpers umfaßt, und wobei wenigstens ein Arzneimittel in Form eines biologisch abbaubaren vernetzten Polymeren und biologisch abbaubaren Copolymeren vorliegt, das kovalent mit dem Grundkörper verbunde ist.

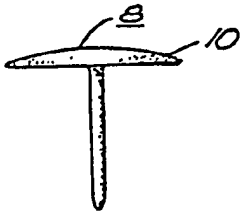


FIG. 1

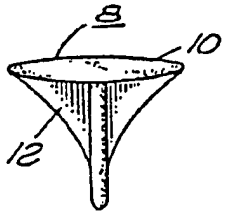


FIG. 2

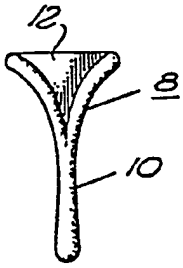


FIG. 3

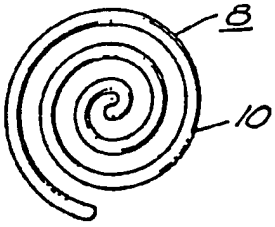


FIG. 4

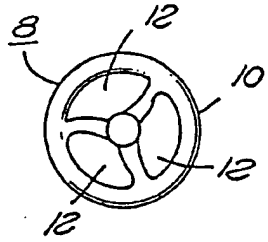


FIG. 5